

The impact of physical exercise on sensor performance of the Abbott Freestyle® Libre intermittently-viewed continuous glucose monitoring (iCGM) system in people with type 1 diabetes – a randomised cross-over trial

Short title: iCGM and exercise in type 1 diabetes

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Novelty statement:

- The Abbott Freestyle® Libre intermittently-viewed continuous glucose monitoring (iCGM) system is known to track changes in the interstitial glucose with sufficient accuracy compared to blood glucose in real-life conditions
- Our data revealed significant limitations in iCGM performance during physical exercise in people with type 1 diabetes

- The overall median absolute relative difference (interquartile range) was 22%(13.9-29.7%), during hypoglycaemia 36.3%(24.2-45.2%), euglycaemia 22.8% (14.6-30.6%) and hyperglycaemia 15.4%(9-21%)
- From a clinical point of view iCGM can only be used as an adjunct to blood glucose measurements to reduce the risk of glycaemic disturbances during physical exercise

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Abstract

Aims To evaluate the sensor performance of the Abbott Freestyle® Libre intermittently-viewed continuous glucose monitoring (iCGM) system to reference blood glucose levels during moderate-intensity exercise while on either full or reduced basal insulin dose in people with type 1 diabetes (T1DM).

Methods Ten participants with T1DM (4 women, age 32.1±9.0 years, BMI 25.5±3.8 kg/m², HbA_{1c} 55±7 mmol.mol⁻¹ (7.2±0.6%)) exercised on a cycle ergometer for 55 min

at a moderate intensity for five consecutive days at the clinical research facility, on either a usual or a 75% basal insulin dose. After a four-week wash-out period, participants performed the second exercise period with the remaining allocation. During exercise reference capillary blood glucose values were analysed by fully enzymatic-amperometric method and compared to the referring interstitial glucose values. iCGM accuracy was analysed by median absolute relative difference (interquartile range), Clarke error grid and Bland-Altman analysis for overall glucose levels during exercise, stratified for glycaemic ranges and basal insulin dosing scheme ($p < 0.05$).

Results 845 glucose values were available during exercise to evaluate iCGM sensor performance. The overall median absolute relative difference across the glycaemic range was 22%(13.9-29.7%), 36.3%(24.2-45.2%) during hypoglycaemia, 22.8%(14.6-30.6%) during euglycaemia and 15.4%(9-21%) during hyperglycaemia. A usual basal insulin dose was associated with a decreased sensor performance during exercise compared to the reduced basal insulin period (median absolute relative difference: 23.7%(17.2-30.7%) vs. 20.5%(12-28.1%), $p < 0.001$).

Conclusions The iCGM sensor showed diminished accuracy during exercise. Absolute glucose readings derived from the iCGM sensor should be used cautiously and need confirmation by additional finger prick blood glucose measurements.

Keywords iCGM, exercise, type 1 diabetes, accuracy

Introduction

The Abbott Freestyle® Libre intermittently-viewed continuous glucose monitoring (iCGM) system is approved for monitoring glucose concentrations without the need for regular additional finger prick blood glucose measures. iCGM usage is not only convenient but with a median absolute relative difference to reference blood glucose levels of 11.4% in both, people with type 1 (T1DM) and type 2 diabetes the sensor has also shown good accuracy (1). Its regular use is associated with improved glycaemic control (HbA_{1c}), lower risk of- and time spent in hypoglycaemia and less glycaemic variability (2).

Regular physical activity conveys important health benefits for people with T1DM and exercise is advocated (3). However, the increased risk of hypoglycaemia and loss of glucose control discourage people with T1DM to engage in regular exercise (4). iCGM allows glucose measurements more frequently and is believed to help maintaining euglycaemia around exercise. Despite the accurate performance under real-life conditions little data exist on iCGM accuracy during exercise. In a previous study iCGM performance was evaluated around exercise and a mean ARD of $8.7 \pm 5.9\%$ was found (5); however, comparison between iCGM and reference blood glucose levels were only available for a rather small number of measurements in this study.

As pre-exercise bolus and/or basal insulin adjustments are regularly performed in people with T1DM to reduce the risk of hypoglycaemia (3) it seems to be crucial to investigate the impact of background insulin doses on iCGM performance, especially examined during repeated exercise bouts.

This study sought to determine interstitial sensor accuracy during exercise and to explore the impact of alterations in background insulin on consequent interstitial glucose sensor accuracy during exercise in individuals with T1DM.

Participants and Methods

This study is an analysis of a prespecified secondary outcome of a clinical trial registered at the German Clinical Trials Register (DRKS.de; DRKS00013477). The primary outcome “time spent in prespecified glycaemic ranges” was recently published (6). The study protocol was approved by the local ethics committee (29-334 ex 16/17) and local health authority (EudraCT number: 2017-000922-37). The study was performed in a cross-over setting, including a 4-week wash out phase, having the participants randomised to either 100% or 75% of their basal insulin degludec. Each participant undertook 5 days of exercise for each dosing scheme (total of 10 days exercise) with 9 glucose measurements each day during the exercise sessions.

Participants' characteristics

Details of inclusion and exclusion criteria have been described previously (6). Four women and six men were included in this trial with an (mean \pm standard deviation (SD)) age of 31.4 ± 9.0 years, body mass index (BMI) of 25.5 ± 3.8 kg/m², HbA_{1c} of 55 ± 7 mmol.mol⁻¹ ($7.2 \pm 0.6\%$), diabetes duration of 19 ± 10.9 years and a total daily insulin dose of 35 ± 13 IU.

Participants were using insulin degludec (Tresiba, Novo Nordisk A/S, DEN) as a basal insulin and insulin aspart (NovoRapid, Novo Nordisk A/S, DEN) as a bolus insulin for at least three months prior to the trial start. Participants' maximum oxygen uptake (VO_{2max}) was 39 ± 12 mL.kg⁻¹.min⁻¹.

Screening visit

Participants performed a cardio-pulmonary exercise test on a cycle ergometer until maximal exhaustion (7). The first and the second lactate turn points as well as the VO_{2max} were determined to prescribe the exercise intensity for the two exercise

periods. Unblinded iCGM readers and sensors were provided by the study site during the run of the study. Participants were trained on how to use the system and seven participants were already using the iCGM prior to the start of the study.

Trial Visits

It was defined that the iCGM sensor must be worn for longer than 48 hours prior to the first exercise session. If any sensor would have been expired during the run of the trial, then the participants would have been told to change the sensor at least two days before the first exercise session to ensure sensor accuracy. During the run of the trial there was no case in which the participants had to change the sensor during the 5-day exercise period. After randomisation to either 100% or 75% of their usual basal insulin dose, participants exercised on a cycle ergometer for 55 min for five consecutive days in the evening at the clinical research facility. The moderate exercise intensity was set at the midpoint between the first and the second lactate turn points corresponding to $63 \pm 7\%$ of VO_{2max} (6).

Prior to the exercise sessions, participants were told to consume the last pre-exercise carbohydrate rich meal and inject their last bolus insulin at least two hours before the start of the exercise to reduce the influence of glucose fluctuations.

If pre-exercise (-15 min) blood glucose concentration was below 7 mmol.L^{-1} , participants consumed 15 to 30 g carbohydrates via fruit juice or glucose gel (8). This procedure was repeated if blood glucose concentration did not increase above 7 mmol.L^{-1} within 10 min. In case of hypoglycaemia (3.9 mmol.L^{-1}) exercise testing was discontinued and 15 to 30 g carbohydrates were administered until participants glucose reached 7 mmol.L^{-1} .

Measurements

During the exercise sessions, cardio-pulmonary variables were measured continuously. Capillary blood samples were taken from the ear lobe immediately before the exercise session (resting value), after the three minute-warm-up period, every seven minutes during the target workload, as well as after the three minute-recovery period, to determine glucose concentrations as reference values by means of fully enzymatic-amperometric method (Biosen S-line, EKF Diagnostics, GER). The EKF instrument is shown to measure blood glucose accurately and can be used instead of the YSI system (YSI Inc., Yellow Springs, USA) (9). During exercise participants' glucose concentration was measured via iCGM to obtain the accompanied interstitial glucose concentration. At the same timepoint of blood glucose collection from the earlobe a scan was performed with the iCGM reader. Interstitial glucose data were then transcribed from the logbook of the reader.

Statistical analyses

The primary outcome of the study was time spent in euglycaemia and based on the assumption that mean time in euglycaemia is increased by 10% in the 75% basal insulin dosing scheme, which resulted in the requirement for ten participants for the study to detect this difference with an alpha of 0.05 and a power of 0.90 (6).

However, we pre-defined accuracy of interstitial glucose compared to blood glucose as a secondary endpoint. As for each test-to-reference measurement pair the primary endpoint is either success (median absolute relative difference $\leq 15\%$) or failure (median absolute relative difference $> 15\%$), we assumed that the probability of success follows a binomial distribution. The appropriate statistical test to determine whether the probability of success meets the requirement established in the study hypothesis (success rate $> 90\%$) was then a one-sample z-test of proportions. We expected 95% of sensor pairs to meet the criterion (effect size of 0.05). The required

sample size with $\alpha = 0.05$ and a power of 90% is therefore 359 values assessed during exercise testing. Our study was therefore also adequately powered for the analysis of this secondary outcome. iCGM sensor performance was evaluated by median absolute relative difference (interquartile range), Clarke error grid and Bland-Altman analysis for overall glucose values immediate before and during exercise and stratified for glycaemic ranges (hypoglycaemia: ≤ 3.9 mmol.L⁻¹, euglycaemia: 4.0–9.9 mmol.L⁻¹, hyperglycaemia: ≥ 10 mmol.L⁻¹). Influence of basal insulin dose (100% vs. 75% basal insulin dose) and the first vs. last phase of the exercise periods (first two days vs. last two days) on sensor performance were analysed by means of Wilcoxon matched-pairs signed rank test for median absolute relative difference ($p < 0.05$).

Results

Immediately prior to the start of exercise testing, iCGM performance under resting condition with 90 points of comparison was found with an overall median absolute relative difference of 13.7% (4.7–17.3%), 14.9% (3.6–18.6%) for the 75% basal insulin dose and 12.4% (6.8–16.7%) for the 100% basal insulin dose. Time spent in glycaemic ranges given as percentage of total time was similar between 75% and 100% dosing scheme: hypoglycaemia $3 \pm 2\%$ vs. $4 \pm 2\%$, euglycaemia $77 \pm 16\%$ vs. $81 \pm 15\%$ and hyperglycaemia $20 \pm 13\%$ vs. $15 \pm 7\%$ ($p > 0.05$). In total we observed 7 hypoglycaemic episodes in 6 participants, 3 in the 100% dosing scheme and 4 in the 75% dosing scheme that were treated each with 24 ± 9 g liquid glucose during the exercise sessions. The rate of change in glucose for the entire observational period was found at 0.054 mmol.L⁻¹.min⁻¹, 0.051 mmol.L⁻¹.min⁻¹ for 100% basal insulin dose and 0.057 mmol.L⁻¹.min⁻¹ for the 75% basal insulin dose. Overall, 57% of blood glucose levels showed a rate of change of below 0.1 mmol.L⁻¹.min⁻¹ and 36% showed a rate of change of below 0.06 mmol.L⁻¹.min⁻¹. For blood glucose measured by the EKF system we

found an inter-individual coefficient of variation of 34% and an intra-individual coefficient of variation of 33% during exercise testing. iCGM measured glucose revealed an inter-individual coefficient of variation of 32% and an intra-individual coefficient of variation of 31% during exercise testing.

Out of potentially 900 points of comparisons, 845 points were available as the iCGM did not display values in 10 cases (1%) and one participant did not perform the second exercise period due to personal reasons. Carbohydrate intake per participant per exercise session was similar for the full basal insulin dose (100%) in comparison to the reduced basal insulin dose (75%) during exercise (36(9–66 g) vs. 36(9–62 g), $p=0.78$). Bland-Altman analysis and Clarke error grids for the overall glycaemic range during exercise, as well as Clarke error grids zone percentages and median absolute relative difference at different levels of glycaemia (hypo-, eu- and hyperglycaemia) are presented in table1 (Bland-Altman and Clarke error grids) and figure 1 (Clarke error grids).

Overall the median absolute relative difference across the glycaemic range during exercise was 22%(13.9–29.7%), during exercise-induced hypoglycaemia 36.3%(24.4–45.2%), during euglycaemia 22.8%(14.6–30.6%) and in periods of hyperglycaemia 15.4%(9–21%). Continuation of the full basal insulin dose during the exercise week was associated with impaired sensor performance in comparison to a reduced basal insulin dose (75%) (median absolute relative difference: 23.7%(17.2–30.7%) vs. 20.5%(12–28.1%), $p<0.001$) despite similar mean blood glucose concentrations (7.4 ± 2.4 mmol.L⁻¹ vs. 7.5 ± 3.0 mmol.L⁻¹, $p=0.73$) and similar blood glucose decreases ($\Delta BG_{\text{start-end exercise}}$: 2.82 ± 0.59 mmol.L⁻¹ vs. 3.13 ± 0.42 mmol.L⁻¹, $p=0.19$).

Bland-Altman analysis revealed that the iCGM system reported higher glucose levels than the reference capillary blood glucose concentration (bias 1.95, 95% limits of agreement from -0.98 to 4.89 mmol.L⁻¹). A reduction in basal insulin dose (75% basal

dose) during the exercise week resulted in numerically less bias and limits of agreements as compared to continuation of the full basal insulin dose (1.69, -1.28 to 4.67 mmol.L⁻¹ vs. 2.24, -0.56 to 5.05 mmol.L⁻¹).

The overall clinical performance analysed via Clarke error grids was found at 76% of values in zone A, 22% in zone B and 2% in zone D, with similar results when data were stratified for basal insulin dose (Figure 1).

The analysis of the first vs. the last exercise period on iCGM performance (median absolute relative difference) resulted in a decrease of accuracy in the full basal insulin dose ($p=0.01$) but not for the 75% basal insulin dose ($p=0.15$).

Discussion

This study revealed that the accuracy of the iCGM system measured glucose was distinctively reduced compared to capillary glucose during moderate-intensity exercise. This is a significant finding given the fact that blood glucose was kept within a well-controlled range without large decreases in blood glucose during exercise due to small amounts of exogenous carbohydrate intake. Where glucose concentrations fell to hypoglycaemic levels a median absolute relative difference of 36.3%(24.2–45.2%) strongly suggests that this device should only be used as an adjunct to blood glucose measurements during exercise. Additionally, early acting on trend arrows provided by the system can be used as a supportive tool to reduce the risk of exercise-induced hypoglycaemia.

An overestimation of iCGM values in comparison to blood glucose reference values was demonstrated by Bland-Altman analysis and this overestimation might increase potential for wrong therapeutic decisions. Our results are in contrast with findings from a previous work of our research team that evaluated the iCGM system to be accurate during exercise testing with a mean ARD of $8.7\pm 5.9\%$ and a Parks error grid of 100%

of values in zone A (5). These differences in findings might be based on the low number of comparison points ($n=13$) and the short duration of exercise (2x15 minutes) performed in the previous study. One could speculate that exercise induced changes in subcutaneous blood flow and larger glucose swings during exercise might at least partly explain the higher median absolute relative difference compared to non-exercise studies.

In our analysis the basal insulin dose was associated with iCGM performance during exercise. A regular basal insulin dose was associated with a decrease in sensor accuracy.

Interestingly, when comparing the devices' performance by means of the continuum of exercise tests (first exercise phase vs. last exercise phase) only for the regular basal insulin dose the accuracy decreased. Whether those associations are reproducible or just a play of chance remains to be elucidated.

The physiological response to higher circulating insulin levels combined with exercise might impact the dynamics of blood glucose changes, with subsequent increasing discrepancy between blood and interstitial glucose values. To overcome this lag time and to reduce the risk of inadequate therapy decisions, an exercise-related algorithm could improve sensor performance (10). However, a recent study in people with T1DM running on continuous subcutaneous insulin infusion showed that a 50% reduction in basal rate 1 hour prior to the start of exercise testing did not significantly reduce free circulating insulin during exercise (11). As shown previously the sensor performance is depending on the rate of change in glucose concentration (12). Under stable conditions and under rates of change between -0.05 to $0.05 \text{ mmol.L}^{-1}.\text{min}^{-1}$ sensor performance revealed a median absolute relative difference of 8.5%. In our study the rate of change can be interpreted as less influential on the results since the rate of

change was found at 0.051 mmol.L⁻¹.min⁻¹ for 100% basal insulin dose and 0.057 mmol.L⁻¹.min⁻¹ for 75% basal insulin dose.

Our study is limited since we did not standardise the timepoint of the last pre-exercise bolus insulin injection that might have influenced sensor performance due to the combination of the insulin sensitising effect of exercise and bolus insulin action. Additionally, despite being shown that blood glucose collected from earlobe in comparison to fingertip did not result in clinically relevant differences under resting conditions (13), a bias of sampling sites might be existing especially during exercise (14). Direct comparability of different blood glucose collection sites is therefore challenging.

Although previous research found that the iCGM system is accurate during real life conditions and improve glycaemic control (1,2,5,15), during exercise the accuracy for absolute glucose values measured is only moderate and additional finger prick glucose measurements are required. In comparison to a previous study performing exercise with a similar mean exercise intensity using the Medtronic Enlite™ sensor (Medtronic Diabetes, USA) the mean absolute relative difference was found at 12.8% (16). However, trend arrows of iCGM providing information about velocity of glucose changes could still be of value during exercise.

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Table 1 Median absolute relative difference (interquartile range) and Bland-Altman analysis during exercise. Median absolute relative difference is defined as [(sensor glucose – reference blood glucose) / reference blood glucose] expressed as a percentage. Median absolute relative difference indicates absolute values of difference and thus ignores the direction of the measurement error but indicate the size of the error expressed as percentage error.

		iCGM accuracy
Median absolute relative difference	Overall	22.0% (13.9 – 29.7%) (n = 845)
	Hypoglycaemia (≤ 3.9 mmol.L ⁻¹)	36.3% (24.2 – 45.2%) (n = 30)
	Euglycaemia (4.0 – 9.9 mmol.L ⁻¹)	22.8% (14.6 – 30.6%) (n = 668)
	Hyperglycaemia (≥ 10 mmol.L ⁻¹)	15.4% (9 - 21%) (n = 147)
	100% basal insulin dose (19 ± 4 IU)	23.7% (17.2 – 30.7%) (n = 400)
	75% basal insulin dose (14 ± 3 IU)	20.5% (12 – 28.1%) (n = 445)
	First exercise period 100% basal insulin dose (19 ± 4 IU)	22.1% (17.2 – 29.2%) (n = 138)
	Last exercise period 100% basal insulin dose (19 ± 4 IU)	24.9% (16.1 - 33%) (n = 142)
	First exercise period 75% basal insulin dose (14 ± 3 IU)	20.4% (11.7 – 28.2%) (n = 180)
	Last exercise period 75% basal insulin dose (14 ± 3 IU)	20.4% (13 – 27.1%) (n = 174)
Bland-Altman	Overall	1.95 (-0.99 – 4.89 mmol.L ⁻¹) (n = 845)
	100% basal insulin dose (19 ± 4 IU)	2.24 (-0.56 – 5.05 mmol.L ⁻¹) (n = 400)
	75% basal insulin dose (14 ± 3 IU)	1.69 (-1.28 – 4.67 mmol.L ⁻¹) (n = 445)

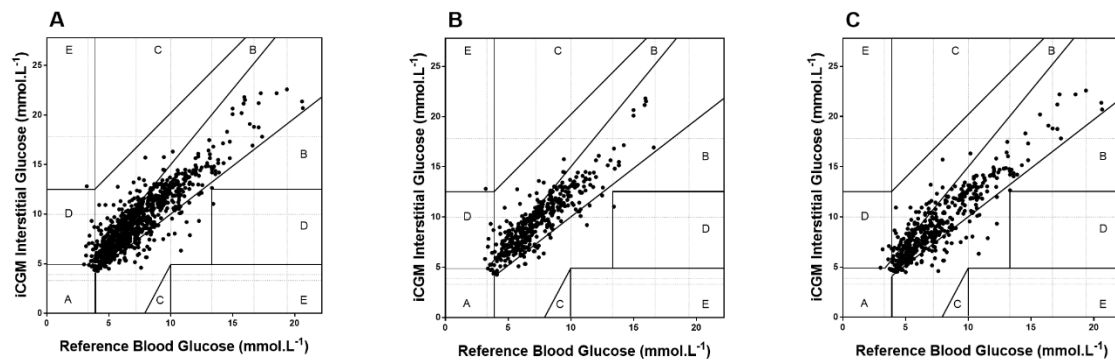
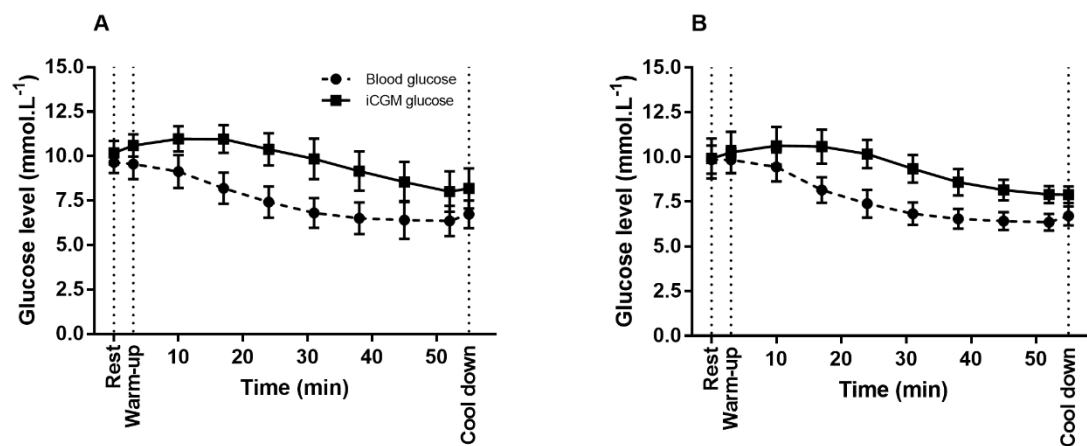
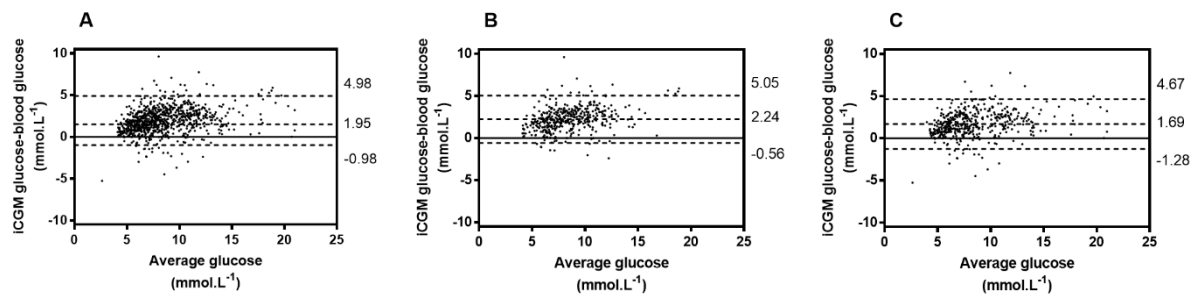


Figure 1 Clarke error grids for overall- (A), 100% basal insulin dose- (B) and 75% basal insulin dose-glucose values (C). The x-axis displays reference blood glucose values (mmol.L⁻¹), the y-axis presents the values measured by the iCGM system (mmol.L⁻¹). The grid is divided into zones showing the degree of risk caused by erroneous measurements: zone A means no effect on clinical action; zone B represents altered clinical action—small or no significant effect on clinical outcome; zone C represents altered clinical action—probable to affect clinical outcome; zone D means altered clinical action—could have significant medical risk; and zone E represents altered clinical action—could have dangerous consequences.

Supporting Information



Supporting information 1 Mean and SD blood glucose and iCGM glucose responses to the exercise session for (A) 100% basal insulin dose and (B) 75% basal insulin dose.



Supporting information 2 Bland–Altman plots for (A) overall exercise sessions, (B) 100% basal insulin dose and (C) 75% basal insulin dose. The x-axis represents the average of blood glucose reference and iCGM values, the y-axis represents the difference (iCGM – blood glucose). The long-dashed lines indicate bias and the 95% limits of agreement.